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Synthesis of Enniatin-like Cyclic Depsipeptides via Direct Amide Cyclization

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The synthesis of several 18-membered cyclodepsipeptides with an alternating sequence of α,α -disubstituted α -amino acid and α -hydroxy acid (compounds **14a-e**) is described. The ring closure *via* macrolactonization was accomplished by treatment of a diluted suspension of the corresponding linear precursors **12a-e** in toluene with HCl-gas, *i.e.*, the so-called ‘direct amide cyclization’. The incorporation of the α,α -disubstituted α -amino acids was achieved *via* the ‘azirine/oxazolone method’ with 2*H*-azirin-3-amines of type **6** and **9** as building blocks. The structure of the cyclic depsipeptide **14a** was established by X-ray crystallography.

1. Introduction. – Cyclic depsipeptides are peptide analogues in which one or several lactam bonds of the cyclic skeleton are displaced by lactone bonds. The cyclization of these compounds is usually the most demanding step in their synthesis. Several successful cyclizations *via* ester bond formation (lactonization) have been reported [1-3], but ring closure *via* formation of an amide bond (lactamization) [4-6] is usually easier and therefore preferred [7].

Cyclization of a peptide or depsipeptide reduces its conformational freedom. This constraint can be increased further if α,α -disubstituted α -amino acids are incorporated into the peptide chain [8], and limiting the flexibility often results in higher receptor-binding affinities [7]. Effective methods for the introduction of α,α -disubstituted α -amino acids and subsequent ring closure to give a cyclic depsipeptide are therefore of interest. A useful cyclization method for depsipeptides containing a C-terminal α,α -disubstituted α -amino acid, the so-called ‘direct amide cyclization’ method, has been developed in our laboratory [9-20]. The basic concept is shown in *Scheme 1*: if an amide of type **1** is treated with dry HCl-gas, the corresponding 1,3-oxazol-5(4*H*)-one derivative **2** is formed *via* ring closure and elimination of dimethylamine hydrochloride. In the absence of other nucleophiles, a ring enlargement to yield the cyclic product **3** occurs by an intramolecular attack of the ω -hydroxy group of the intermediate oxazolone at the lactone group.

Scheme 1

Several cyclic depsipeptides containing one hydroxy acid and several α,α -disubstituted α -amino acids have been prepared by using this cyclization method [9-17]. A subgroup among the depsipeptides consists of the so-called regular cyclodepsipeptides [21][22], whose cyclic core shows an alternating pattern of α -amino acids and α -hydroxy acids. Some of these regular cyclodepsipeptides show high biological activity, like the antibiotics valinomycin [23-25] and the enniatins [26], which act as ionophores [27]. Some 12-membered regular cyclodepsipeptides, also containing α,α -disubstituted α -amino acids, have been synthesized in our group *via* 'direct amide cyclization' [11]. It was therefore of interest to investigate whether 18-membered regular cyclodepsipeptides of the 'enniatin type', composed of α -amino acids and α -hydroxy acids, could also be synthesized by this method. Some preliminary experiments have already been carried out [28]. The incorporation of the α,α -disubstituted α -amino acid units can be achieved *via* the elegant and efficient 'azirine/oxazolone method' that has been developed in our group [29] and successfully applied to the synthesis of peptaibols [30-35], endothiopeptides [36-39] and conformationally restricted cyclic peptides [40-44].

2. Results and Discussion. – 2.1. *Synthesis of the Linear Precursors.* The desired linear precursors **12** were synthesized according to a strategy similar to that reported for the 12-membered depsipeptides [11] (see also [28]). The same approach has been used in the synthesis of a 24-membered cyclic depsipeptide [45][46].

Three different α -hydroxy acids, **4a–4c**, and six different 2*H*-azirin-3-amines **6a–6c** and **9a–9c**, which are the building blocks for the α,α -disubstituted α -amino acids,

were used to prepare the precursors for the ‘direct amide cyclization’. An overview of the syntheses is shown in *Scheme 2*.

Scheme 2

As the 2-benzyl-2-methyl-2*H*-azirin-3-amines **6c** and **9c** were employed as racemates, the synthesis yielded the precursor **12c** for the macrolactonization as a racemic mixture of four diastereoisomers.

2.2. Macrolactonizations. With the linear precursors **12a-e** in hand, we studied their cyclizations *via* the ‘direct amide cyclization’ method (*Scheme 3*). Initial optimization of the reaction conditions was undertaken by using compound **12a**. The solvent and the reaction temperature were adopted from the protocols of the cyclizations that gave similar 12-membered cyclodepsipeptides [11].

Scheme 3

A 10-15 mM solution of **12a** in toluene was treated with a stream of dry HCl gas at 100°. The reaction mixture was then allowed to cool to room temperature while bubbling N₂ through it. Evaporation of the solvent gave a mixture of the crude product and dimethylamine hydrochloride, which was separated by column chromatography.

It turned out that longer reaction times reduce the yield of the desired product, probably due to decomposition of the product as well as of the starting material, caused

by the limited stability of the ester bonds (see below). On the other hand, short reaction times result in a lower conversion of the starting material, so a compromise for the reaction time had to be found. The treatment with HCl gas over a period of 4.5 min proved to be the optimum, yielding 27% of the macrocycle **14a**. The ^1H - and ^{13}C -NMR-spectra of **14a** clearly show that a single isomer is present and epimerization had occurred at one of the three stereogenic centers. Epimerization of one of the α -hydroxy acids leads to three topologically different α -hydroxy acid units, as well as three different α,α -dimethyl α -amino acid units in **14a**. Indeed, the NMR-spectra showed three different sets of signals instead of one, as would be expected without epimerization. On the other hand, it is worth mentioning that **14a** is optically active. The structure and the relative configuration of the recrystallized **14a** were established by X-ray crystallography, and the molecular structure confirms the configuration with one inverted stereogenic center (*Figure*).

Figure. *ORTEP Plot [47] of the molecular structure of one of the symmetry-independent molecules of 14a (30% probability ellipsoids; arbitrary numbering of atoms, most H-atoms omitted for clarity).*

The crystals of **14a** are enantiomerically pure and there are two molecules of the same enantiomer in the asymmetric unit, however the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was chosen arbitrarily. This enantiomer has the (3*R*,9*S*,15*S*)-configuration²), but due to the absence

²) Arbitrary numbering of atoms used in the *Figure*.

of a strong anomalous scatterer in the structure, this enantiomer cannot be distinguished crystallographically from the (3*S*,9*R*,15*R*)-enantiomer. Although all sites were expected to have the (*S*)-configuration, it is not possible to say if one site has inverted, or two. The two symmetry independent molecules have almost identical conformations, with the only difference being a small rotation in the orientation of the phenyl ring of the benzyl substituent at C(15). Each of the two symmetry-independent molecules has the same pattern of H-bonds. Two of the amide groups in each molecule form a total of three intramolecular H-bonds. One of these is an interaction with the amide O-atom of the next amide unit around the macrocyclic ring, thereby giving rise to a 10-membered loop with a graph set motif [48] of S(10). The other two intramolecular interactions emanate from the same N-atom as weak bifurcated interactions with the ether O-atoms of the ester groups on either side of this N-atom, thereby creating small loops with graph set motifs of S(5). The third amide group forms an intermolecular H-bond with an amide O-atom of an adjacent symmetry-unrelated molecule, thereby linking molecules A and B alternately into extended chains which run parallel to the *z*-axis with an ...A...B...A...B... sequence that yields a binary graph set motif of $C^2_{,2}(20)$.

We used the optimized conditions mentioned above for the cyclization of the other linear precursors **12b-12e**. In the case of **12b**, which differs from **12a** only in the substituent on the α -amino acid units being a cyclopentane ring instead of the two Me groups, the desired depsipeptide **14b** was obtained in a yield of 25%, which is comparable with the cyclization yield of **12a**. Again, ^1H - and ^{13}C -NMR-spectra show that complete epimerization at one of the stereogenic centers had occurred.

Compared with **12b**, the third hydroxy acid of the cyclization precursor **12e** (counting from the amide terminus) bears a Me group instead of the benzyl residue ($R = \text{Me}$, $R^1 = \text{PhCH}_2$). This should allow the (otherwise undistinguishable) stereogenic centres in the cyclized product to be identified, provided that this variation still leads to the same phenomenon of complete inversion at one stereogenic center. The ring closing reaction was accomplished successfully by applying the same conditions as before, and the corresponding depsipeptide **14e** was isolated in 33% yield. The ^1H - and ^{13}C -NMR-spectra of **14e** showed that this compound was again formed as a single diastereoisomer. As the configuration of **14e** cannot be determined by means of NMR-spectroscopy, we tried to establish the structure by X-ray crystallography. Unfortunately, we were unable to grow crystals suitable for a structure determination, so the relative configurations of the chiral centers in **14e** could not be determined. Therefore, this experiment could not clarify the proposal that the stereogenic center adjacent to the oxazolone ring of the intermediate **13** was inverted during the cyclization.

The linear precursor **12d** used for the next ring closure differs from **12a** in that there is no benzyl unit next to the ω -hydroxy group. The cyclization experiment therefore shows the difference between a primary and a secondary OH-group attacking the oxazolone intermediate. When the cyclization was carried out under the same conditions as for **12a** and **12b**, the depsipeptide **14d** could be isolated with a significantly higher yield of 43%, and less by-products were formed. In contrast to **14a** and **14b**, the macrolactone **14d** was formed as a mixture of two diastereoisomers, most likely due to the configurational instability of the first stereogenic center (counting from the former amide terminus (see below)).

The linear depsipeptide **12c** also bears a primary ω -hydroxy group and is substituted with benzyl groups at the α -amino acid units to ensure the UV-activity of the corresponding macrocycle. Ring closure under the usual conditions gave the desired cyclodepsipeptide **14c** in 46% yield, which is comparable with that of ring **14d**. Since the linear precursor **12c** was synthesized as a racemic mixture of different diastereoisomers, the reaction yielded **14c** as a mixture of the two possible diastereoisomers in racemic form.

Due to the lower steric hindrance, linear precursors with a primary ω -hydroxy group seem to be more appropriate for the ‘direct amide cyclization’ method than those bearing a secondary hydroxy group. The yields, ranging from 25 to 46%, are comparable with those of other cyclization methods for macrolactones of similar ring sizes. A possible explanation for the moderate yields in the present study could be the instability of the ester bonds of the cyclization precursors under the conditions of the ‘direct amide cyclization’. This could indeed be shown by a control experiment, in which the HCl-treatment was carried out in the presence of MeOH as an external nucleophile. Under these conditions, amide **10a**, which does not contain ester bonds, was converted into the corresponding methyl ester quantitatively. On the other hand, the analogous treatment of **12a** resulted in a lower yield of products, and a mixture of the homologous esters was obtained (*cf.* also [46]) (*Scheme 4*).

Scheme 4

Most likely, the depsipeptide bonds are cleaved *via* the intramolecular formation of 1,3-oxazol-5(4*H*)-ones as intermediates under the conditions of the ‘direct amide cyclization’. Alternatively, an intermolecular attack of the free hydroxy group of the corresponding linear precursor could cleave one of the ester bonds, thereby further reducing the yields of the cyclodepsipeptides.

As already mentioned, cyclodepsipeptides **14a** and **14b** were formed as single diastereoisomers with inverted configuration at one of the stereogenic centers. It is already known from the synthesis of 6-membered cyclic depsipeptides that the ‘direct amide cyclization’ can lead to a partial epimerization at the center in the α -position to the protonated oxazolone [10]. However, complete isomerization to give only the other diastereoisomer was surprising, as one would expect a mixture of diastereoisomers to be obtained. Therefore, we decided to examine at which position the inversion occurs. For this purpose, we subjected the optically active amide segments **10b** and **15** to the ‘direct amide cyclization’ conditions that were used for the syntheses of the 18-membered macrocycles (*Scheme 5*).

Scheme 5

In the case of amide **10b**, which is able to form a 1,3-oxazol-5(4*H*)-one, the expected diketopiperazine **16** was formed as a racemate. On the other hand, amide **15**, which cannot form an oxazolone, proved to be configurationally stable under these conditions. Even after a prolonged HCl-treatment (30 min) at 100°, the other enantiomer

could not be detected³). These results indicate that the only chiral center in the linear precursors **12**, where the observed epimerization occurs, is the first one, counting from the former amide terminus, *i.e.* the stereogenic center in the α -position of the intermediate oxazolone.

Although the position of the inversion of the configuration was clarified, the reason for the formation of a single diastereoisomer of the depsipeptide was not clear. In order to determine if this phenomenon is an attribute of the ‘direct amide cyclization’ or if other macrolactonization methods would show a similar effect, a test reaction using the *Corey-Nicolaou* method [49] was carried out. In a control experiment to synthesize diketopiperazine **16**, almost no racemization occurred. Therefore, amide **12b** was hydrolyzed to give the corresponding carboxylic acid **17b** by treatment with 3N HCl in THF/H₂O (*Scheme 6*). Subsequent reaction with Ph₃P and 2,2’-dipyridyl disulfide (DPS) in CH₂Cl₂ did not yield the desired cyclodepsipeptide **14b**, and only decomposition products were found. If the same reaction sequence was performed with the epimer **12b’** (prepared analogously to **12b** according to *Scheme 2*) under identical conditions, the macrocycle **14b** could be isolated in 16% yield (*Scheme 6*)⁴.

Scheme 6

³) Amide **15** and diketopiperazine **16** were analyzed by means of HPLC on a chiral column with the racemic compounds as standards.

⁴) NMR-spectra of **17b** and **17b’** showed that no epimerization occurred during the acid-catalyzed amide hydrolysis.

This result indicates that the precursor with one inverted configuration is more favorable for the cyclization step than the homochiral analogue. Probably, the epimerized precursor promotes a conformation that is more suitable for the ring closure.

3. Conclusions. – Five different 18-membered regular cyclodepsipeptides of the enniatin type, which contain α,α -disubstituted α -amino acids, have been synthesized. The efficient ‘azirine/oxazolone method’ was used to incorporate the sterically demanding amino acid units into the linear precursors. The cyclizations *via* macrolactonization were achieved by the ‘direct amide cyclization’ method and gave the desired products with yields ranging from 25 to 46%. The ring closure of precursors with a primary ω -hydroxy group gave the products in higher yields than those with the corresponding compounds bearing a secondary OH-group. Cyclizations of the two similar compounds **12a** and **12b**, possessing three α -substituted α -hydroxy acids, lead to cyclic depsipeptides with one epimerized chiral center. The results of some control experiments indicate that the epimerization occurs at the adjacent chiral center of the intermediate 1,3-oxazol-5(4*H*)-one. The structure of the cyclic depsipeptide **14a** has been determined by X-ray crystallography.

Experimental Part

1. *General*. See [18]. Solvents were purified by standard procedures. Thin-layer chromatography (TLC): *Merck* TLC aluminium sheets, silica gel 60 F_{254} . Flash chromatography (CC): *Uetikon-Chemie* ‘Chromatographiegel’ C-560. M.p.: *Büchi* 540 apparatus, uncorrected. IR Spectra: *Perkin-Elmer Spectrum one* spectrometer; in CHCl_3 , unless otherwise stated, absorption bands in cm^{-1} . ^1H -NMR (300 and 600 MHz) and ^{13}C -NMR (75.5 and 151 MHz) spectra: *Bruker ARX-300* and *DRX-600* instrument, in CDCl_3 at 300 K, TMS as internal standard, $^{\text{TM}}$ in ppm, coupling constants J in Hz. ^{13}C -signal multiplicity from DEPT spectra. Mass spectrometry (MS): *Finnigan MAT 90* for electron-impact ionization (EI), *Finnigan SSQ-700* for chemical ionization (CI, with NH_3) and electrospray ionization (ESI, in $\text{MeOH} + \text{NaI}$).

The 2*H*-azirin-3-amines **6a–c** and **9a–c** were prepared according to standard procedures (*cf.* [29] and refs. cited therein). 2-(Benzyloxy)acetic acid (**5b**) was prepared according to [50], and 2-(benzyloxy)propanoic acid (**5c**) was prepared according to [51]. All other products used were commercially available. The syntheses and spectroscopic data of **5a**, **7a**, **8a**, **10a**, **11a** and **12a** are described in [45] (see also [46]).

General procedure 1 (GP 1). *Reaction of azirines 6 and 9 with acids 4 and 5*. To a soln. of the acid in MeCN was added a soln. of the azirine in MeCN. The mixture was stirred at r.t. for 16 h, evaporated, and the residue was purified by column chromatography (CC).

General procedure 2 (GP 2). *Hydrolysis of amides 7 to acids 8*. A soln. of **7** (3.0 mmol) in THF (15 ml) was treated with aq. 6N HCl (15 ml) and stirred for 6 h at r.t. Subsequent addition of aq. 2N HCl (15 ml), extraction with Et_2O , drying (MgSO_4), and evaporation gave **8** in pure form.

*General procedure 3 (GP 3). Esterification of acids **8** with alcohols **10**, **11** and subsequent hydrogenolysis of the benzyl ether:* A soln. of **8** and 1.0 equiv. of 1,1'-carbonyldiimidazole (CDI) in dry THF was stirred for 2 h under N₂. The corresponding alcohol was then added, followed by 10 drops of a sodium imidazolidate suspension (freshly prepared by the reaction of 45 mg of a 60% suspension of NaH in mineral oil with 73 mg of imidazole in 3 ml of dry THF). After the completion of the reaction (TLC, 2-16 h), the solvent was evaporated and the mixture purified by column chromatography. The coupling product was then dissolved in THF/*i*PrOH 1:1, a catalytic amount of Pd on charcoal was added, and the suspension was stirred under a H₂ atmosphere until completion of the reaction (TLC). The mixture was then filtered over *Celite*, evaporated and purified by CC.

*General procedure 4 (GP 4). Cyclization of the linear precursors **12a-e** and **10b**.* A soln. of **12a,b,c,d,e** or **10b** in toluene was treated with a strong stream of dry HCl-gas for 4.5 min at 100°. The mixture was then allowed to cool to r.t., while bubbling N₂ through it. Evaporation of the solvent and purification by column chromatography gave the corresponding cyclodepsipeptide.

*2. Synthesis of Linear Precursors. – 2.1. 1-((S)-2-Benzoyloxy-3-phenylpropanoyl-amino)-N-methyl-N-phenylcyclopentanecarboxamide (**7b**):* According to GP 1, **5a** (1.0 g, 3.9 mmol) in MeCN (20 ml), **6b** (780 mg, 3.9 mmol) in MeCN (5 ml), 14 h, CC (SiO₂, hexane/Et₂O 1:1): 1.62 g (91%) of **7b**. White powder. M.p. 106–107°. ¹H-NMR: 1.30-1.70, 2.20-2.30, 2.40-2.50 (3*m*, 6H + 1H + 1H, (CH₂)₄); 2.92 (*dd*, *J* = 7.6, 14.1, 1 H of PhCH₂C); 3.15 (*dd*, *J* = 3.8, 14.1, 1 H of PhCH₂C); 3.22 (*s*, MeN); 3.83 (*dd*, *J* = 3.8, 7.6,

CH₂CHO); 4.10, 4.29 (2*d*, *J* = 11.8, PhCH₂O); 7.00-7.40 (*m*, 10 arom. H, NH). EI-MS: 456, (3, *M*⁺), 350 (21, [*M* – Ph(Me)N]⁺), 322 (43, [*M* – CON(Me)Ph]⁺), 107 (67, C₇H₇O⁺), 91 (100, C₇H₇⁺). [α]_D²⁵: –61.4 (*c* = 1.1, CHCl₃).

2.2. 2-[(2-Benzoyloxy)acetylamino]-2,N-dimethyl-3,N-diphenylpropanamide (**7c**):

According to GP 1, **5b** (1.31 g, 7.9 mmol) in MeCN (30 ml), **6c** (2.2 g, 7.9 mmol) in MeCN (5 ml), 14 h, CC (SiO₂, hexane/^tBuOMe 1:1): 2.67 g (81%) of **7c**. Yellowish oil. IR: 3405*m*, 3010*s*, 1770*w*, 1680*s*, 1635*s*, 1595*m*, 1520*s*, 1495*m*, 1380*s*, 1110*s*, 700*m*. ¹H-NMR: 1.49 (*s*, Me); 3.26 (*s*, MeN); 3.23, 3.43 (2*d*, *J* = 13.7, PhCH₂C); 3.60 (*s*, PhCH₂O); 4.21, 4.29 (2*d*, *J* = 11.7, CH₂CO); 6.60 (*s*, NH); 7.00-7.40 (*m*, 15 arom. H). ¹³C-NMR: 24.2 (*q*, Me); 41.5 (*q*, MeN); 43.1 (*t*, PhCH₂C); 60.7 (*s*, PhCH₂(Me)C); 69.7, 73.0 (2*t*, PhCH₂OCH₂); 126.8, 127.4, 127.5, 127.6, 127.9, 128.1, 128.3, 129.1, 130.4 (9*d*, 15 arom. CH); 136.2, 136.8 (2*s*, 2 arom. C); 144.6 (*s*, arom. CN); 168.3, 172.0 (2*s*, 2 C=O). CI-MS: 417 (60, [*M* + 1]⁺), 310 (100, [*M* – Ph(Me)N]⁺).

2.3. 2-[(2-Benzoyloxy)acetylamino]-2,N-dimethyl-N-phenylpropanamide (**7d**):

According to GP 1, **5b** (2.86 g, 17.2 mmol) in MeCN (60 ml), **6a** (3.0 g, 17.2 mmol) in MeCN (15 ml), 14 h, CC (SiO₂, hexane/Et₂O 1:6): 5.33 g (91%) of **7d**. White powder. M.p. 76-79°. ¹H-NMR: 1.51 (*s*, Me); 3.25 (*s*, MeN); 3.67, 4.39 (2*s*, 2 CH₂); 6.63 (br. *s*, NH); 7.20-7.38 (*m*, 5 arom. H). ¹³C-NMR: 26.7 (*q*, Me₂C); 41.3 (*q*, MeN); 57.5 (*s*, Me₂C); 69.7, 73.3 (2*t*, PhCH₂OCH₂); 127.5, 127.7, 127.8, 128.0, 128.4, 129.2 (6*d*, 10 arom. CH); 136.7 (*s*, arom. C); 144.6 (*s*, arom. CN); 168.1, 172.8 (2*s*, 2 C=O).

2.4. 1-[(*S*)-2-(Benzoyloxy)propanoylamino]-N-methyl-N-phenylcyclopentane-carboxamide (**7e**): According to GP 1, **5c** (1.80 g, 10.0 mmol) in MeCN (50 ml), **6b** (2.0 g, 10.0 mmol) in MeCN (10 ml), 14 h, CC (SiO₂, CH₂Cl₂/MeOH 1:6): 3.27 g (86%) of

7d. White powder. M.p. 107-108°. IR (KBr): 3314_s, 2975_m, 2929_m, 2874_m, 1686_s, 1627_s, 1536_m, 1494_s, 1388_m, 1153_m, 1114_m, 1066_w, 1023_w, 770_w, 745_m, 699_m. ¹H-NMR: 1.31 (*d*, *J* = 6.7, Me); 1.48-1.63, 1.64-1.88, 2.30-2.47, 2.50-2.62 (4_m, 2 H each, (CH₂)₄); 3.25 (*s*, MeN); 3.67 (*q*, *J* = 6.7, MeCH); 4.21, 4.41 (2_d, *J* = 11.5, PhCH₂O); 6.16 (br. *s*, NH); 7.13-7.37 (*m*, 10 arom. H). ¹³C-NMR: 17.04 (*q*, Me); 24.1, 24.2, 38.7, 39.3 (4_t, (CH₂)₄); 40.7 (*q*, MeN); 66.7 (*s*, NCCO); 71.3 (*t*, PhCH₂O); 75.8 (*d*, MeCH); 127.1, 127.2, 127.3, 127.8, 128.3, 129.1 (6_d, 10 arom. CH); 137.3 (*s*, arom. C); 144.9 (*s*, arom. CN); 171.3, 172.3 (2_s, 2 C=O). ESI-MS: 403 (100, [*M* + Na]⁺). [α]_D²⁵: -48.4 (*c* = 1.0, CHCl₃).

2.5. *1-((S)-2-Benzyloxy-3-phenylpropanoylamino)cyclopentanecarboxylic Acid (8b)*: According to GP 2, **7b** (1.37 g, 3.0 mmol) in THF (15 ml), aq. 6N HCl (15 ml): 1.06 g (96%) of **8b**. White powder. M.p. 136-138°. IR: 3414_m, 3066_m, 3021_s, 1713_s, 1675_s, 1513_s, 1454_m, 1239_m, 1090_s. ¹H-NMR: 1.55-1.92, 2.20-2.39 (2_m, 6 H + 2 H, (CH₂)₄); 2.96 (*dd*, *J* = 7.6, 14.1, 1 H of PhCH₂C); 3.16 (*dd*, *J* = 3.6, 14.1, 1 H of PhCH₂C); 4.16 (*dd*, *J* = 3.6, 7.6, CHO); 4.10, 4.29 (2_d, *J* = 11.8, PhCH₂O); 6.94 (*s*, NH); 7.20-7.40 (*m*, 10 arom. H); 10.80 (br. *s*, CO₂H). ¹³C-NMR: 24.4, 36.6, 37.5, 38.8 (4_t, (CH₂)₄); 41.3 (*t*, PhCH₂C); 56.7 (*s*, NCCO); 73.1 (*t*, PhCH₂O); 80.7 (*d*, CHO); 126.5, 127.9, 128.0, 128.1, 128.5, 129.7 (6_d, 10 arom. CH); 136.8, 136.9 (2_s, 2 arom. C); 172.9, 177.6 (2_s, 2 C=O). CI-MS: 368 (100, [*M* + 1]⁺), 274 (9), 108 (6). [α]_D²⁵: -56.8 (*c* 1.0, CHCl₃).

2.6. *2-[(2-Benzyloxy)acetylamino]-2-methyl-3-phenylpropanoic Acid (8c)*: According to GP 2, **7c** (1.25 g, 3.0 mmol) in THF (15 ml), aq. 6N HCl (15 ml): 883 mg (90%) of **8c**. White powder. M.p. 117-118°. IR (KBr): 3363_s, 3030_m, 2887_s, 1715_s,

1670s, 1542s, 1454m, 1211s, 1133s, 995m, 741m, 696m. $^1\text{H-NMR}$: 1.70 (s, Me); 3.35, 3.50 (2d, $J = 13.6$, PhCH_2C); 3.94, 4.02 (2d, $J = 15.6$, PhCH_2O); 4.39, 4.43 (2d, $J = 11.8$, CH_2CO); 7.10-7.40 (m, 10 arom. H); 10.60 (br. s, CO_2H). $^{13}\text{C-NMR}$: 23.1 (q, Me); 41.3 (t, PhCH_2C); 60.6 (s, $\text{PhCH}_2(\text{Me})\text{C}$); 69.3, 73.4 (2t, $\text{PhCH}_2\text{OCH}_2$); 127.0, 127.8, 128.0, 128.3, 128.4, 129.8 (6d, 10 arom. CH); 135.7, 136.6 (2s, 2 arom. C); 170.3, 176.9 (2s, 2 C=O). CI-MS: 328 (100, $[M + 1]^+$).

2.7. 2-[(2-Benzyloxy)acetylamino]-2-methylpropanoic Acid (**8d**). According to GP 2, **7d** (1.02 g, 3.0 mmol) in THF (15 ml), aq. 6N HCl (15 ml): 730 mg (97 %) of **8d**. White powder. M.p. 89-90°. $^1\text{H-NMR}$: 1.60 (s, Me); 4.02 (s, PhCH_2O); 4.62 (s, CH_2CO); 7.05 (s, NH); 7.30-7.40 (m, 5 arom. H); 9.85 (br. s, CO_2H). $^{13}\text{C-NMR}$: 24.6 (q, Me_2C); 56.3 (s, Me_2C); 69.4, 73.7 (2t, $\text{PhCH}_2\text{OCH}_2$); 127.9, 128.2, 128.5 (3d, 5 arom. CH); 136.6 (s, arom. C); 170.2, 177.5 (2s, 2 C=O). CI-MS: 259 (5, $[M + \text{NH}_4]^+$), 252 (100, $[M + 1]^+$). $[\alpha]_D^{25}$: -39.8 (c = 0.7, CHCl_3).

2.8. 1-[(S)-2-(Benzyloxy)propanoylamino]cyclopentanecarboxylic Acid (**8e**): According to GP 2, **7e** (2.20 g, 5.8 mmol) in THF (30 ml), aq. 6N HCl (30 ml): 1.60 g (95%) of **8e**. White powder. M.p. 96°. IR (KBr): 3360s, 2939s, 1706s, 1628s, 1531s, 1418m, 1337m, 1242s, 1191s, 1109s, 1062m, 934m, 773m, 736s, 695m. $^1\text{H-NMR}$: 1.41 (d, $J = 6.8$, Me); 1.69-2.04, 2.20-2.38 (2m, 6H + 2H, $(\text{CH}_2)_4$); 3.99 (q, $J = 6.8$, MeCH); 7.06 (br. s, NH); 7.25-7.38 (m, 5 arom. H); 11.22 (br. s, CO_2H). $^{13}\text{C-NMR}$: 18.39 (q, Me); 24.43, 24.46, 37.10, 37.27 (4t, $(\text{CH}_2)_4$); 65.63 (s, NCCO); 72.15 (t, PhCH_2O); 76.23 (d, CHO); 127.81, 128.08, 128.56 (3d, 5 arom. CH); 137.09 (s, arom. C); 177.44 (s, C=O). ESI-MS: 314 (100, $[M + \text{Na}]^+$). $[\alpha]_D^{25}$: -39.8 (c = 1.0, CHCl_3).

2.9. *1-((S)-2-Hydroxy-3-phenylpropanoylamino)-N,N-dimethylcyclopentane-carboxamide (10b)*: According to GP 1, **4a** (2.0 g, 12.1 mmol) in MeCN (50 ml), **9b** (1.66 g, 12.1 mmol) in MeCN (15 ml), 14 h, CC (SiO₂, CH₂Cl₂/MeOH 30:1): 3.46 g (94%) of **10b**. White powder. M.p. 179-180°. IR: 3407*m*, 3020*m*, 3011*m*, 2964*m*, 2877*m*, 1673*s*, 1632*s*, 1511*s*, 1454*m*, 1393*m*, 1242*m*, 1152*m*, 1086*m*, 1057*m*, 1031*m*, 1005*w*, 905*w*, 842*m*. ¹H-NMR: 1.50-1.90, 2.30-2.50 (2*m*, 6H + 2H, (CH₂)₄); 2.94 (*s*, Me₂N); 2.95 (*dd*, *J* = 7.6, 14.0, 1 H of PhCH₂); 3.21 (*dd*, *J* = 4.0, 14.0, 1 H of PhCH₂); 4.32 (*dd*, *J* = 4.0, 7.6, CHO); 6.72 (*s*, NH); 7.25-7.40 (*m*, 5 arom. H). ¹³C-NMR: 24.1, 24.2, 37.0, 37.2 (4*t*, (CH₂)₄); 37.5 (*q*, Me₂N); 40.3 (*t*, PhCH₂); 66.0 (*s*, NCCO); 72.4 (*d*, CHO); 126.7, 128.4, 129.7 (3*d*, 3 arom. CH); 136.9 (*s*, arom. C); 171.5, 172.1 (2*s*, 2 C=O). CI-MS: 322 (13, [M + NH₄]⁺), 305 (100, [M + 1]⁺). [α]_D²⁵: -40.7 (*c* = 1.1, CHCl₃).

2.10. *2-(2-Hydroxyacetyl-amino)-2,N,N-trimethyl-3-phenylpropanamide (10c)*: According to GP 1, **4b** (2.17 g, 28.6 mmol) in MeCN/THF 5:1 (100 ml), **9c** (5.40 g, 28.6 mmol) in MeCN (15 ml), 14 h, CC (SiO₂, CH₂Cl₂/MeOH 40:1): 6.05 g (80%) of **10c**. White powder. M.p. 149-150°. IR (KBr): 3293*s*, 3064*m*, 1680*s*, 1615*s*, 1550*m*, 1393*m*, 1223*m*, 1096*s*, 701*m*. ¹H-NMR: 1.51 (*s*, Me); 3.00 (*br. s*, Me₂N); 3.30 (*s*, PhCH₂); 3.98 (*s*, CH₂O); 4.30 (*br. s*, OH); 7.00-7.30 (*m*, 5 arom. H); 7.36 (*br. s*, NH). ¹³C-NMR: 22.8 (*q*, Me); 38.1 (*q*, Me₂N); 41.5 (*t*, PhCH₂); 59.5 (*s*, PhCH₂(Me)C); 61.9 (*t*, CH₂O); 126.8, 128.2, 130.2 (3*d*, 5 arom. CH); 136.1 (*s*, arom. C); 171.1, 172.0 (2*s*, 2 C=O). CI-MS: 265 (100, [M + 1]⁺).

2.11. *(S)-1-[1-(Dimethylcarbamoyl)cyclopentylcarbamoyl]-2-phenylethyl 1-[(S)-2-Hydroxy-3-phenylpropanoyl]amino]cyclopentanecarboxylate (11b)*: According to GP 3, **8b** (1.32 g, 3.60 mmol), CDI (583 mg, 3.60 mmol), **10b** (1.09 g, 3.60 mmol), THF

(40 ml), 2 h, CC (SiO₂, CH₂Cl₂/MeOH 50:1): 2.07 g (88%) of **11b**, direct conversion into **13b** without further characterization.

2.12. *[(1-Dimethylcarbamoyl-1-methyl-2-phenylethyl)carbamoyl]methyl 2-[(2-Hydroxyacetyl)amino]-2-methyl-3-phenylpropanoate (11c)*: According to GP 3, **8c** (1.18 g, 3.60 mmol), CDI (583 mg, 3.60 mmol), **10c** (950 mg, 3.60 mmol), THF (40 ml), 2 h, CC (SiO₂, CH₂Cl₂/MeOH 60:1): 1.02 g (59%) of **11c** (mixture of 2 diastereoisomers). White powder. M.p. 84-86°. IR (KBr): 3394_w, 3283_s, 3029_m, 2942_m, 1748_s, 1672_s, 1540_s, 1454_m, 1108_s, 740_m, 702_m. ¹H-NMR: 1.31, 1.46, 1.58, 1.58 (4s, 2 Me); 2.8-3.6 (m, Me₂N + 2 PhCH₂ + 1 H of HOCH₂ + OH); 3.73, 3.76 (2d, J = 16.5, 1 H of HOCH₂); 4.41, 4.43, 4.59, 4.71 (4d, J = 15.6, CH₂CO₂); 6.90-7.40 (m, 10 arom. H, NH); 7.71, 7.88 (2s, NH). ¹³C-NMR: 20.6, 22.0, 22.4, 22.6 (4q, 2 Me); 38.2 (q, Me₂N); 40.5, 40.7, 41.1, 43.1 (4t, 2 PhCH₂); 58.4, 58.9, 60.0, 60.2 (4s, 2 PhCH₂(Me)C); 61.7, 61.8, 63.1, 63.2 (4t, 2 CH₂O); 126.6, 127.1, 127.3, 128.0, 128.2, 128.4, 130.1, 130.3, 130.4 (9d, 10 arom. CH); 134.6, 135.0, 136.5, 136.6 (4s, 2 arom. C); 166.0, 166.2, 171.8, 172.3, 172.4, 172.7, 172.8, 174.7 (8s, 4 C=O). ESI-MS: 989 (30, [2M + Na]⁺), 506 (100, [M + Na]⁺).

2.13. *(S)-1-[1-(Dimethylcarbamoyl)cyclopentylcarbamoyl]-2-phenylethyl 1-[(S)-2-{1-[(S)-2-Hydroxy-3-phenylpropanoyl]amino}cyclopentanecarbonyloxy}-3-phenylpropanoyl]amino]cyclopentanecarboxylate (12b)*: According to GP 3, **8b** (1.32 g, 3.60 mmol), CDI (583 mg, 3.61 mmol), **11b** (2.03 g, 3.60 mmol), THF (40 ml), 16 h, CC (SiO₂, CH₂Cl₂/MeOH 50:1): 2.52 g (85 %) of **11**. White powder. M.p. 117-118°. IR: 3414_m, 3292_s, 3065_m, 3021_m, 2963_m, 2876_m, 1740_s, 1651_s, 1541_s, 1497_m, 1454_m, 1395_m, 1298_m, 1238_s, 1168_s, 1083_s, 1031_m, 969_w, 913_w, 861_w. ¹H-NMR: 1.50-1.92, 1.96-2.58 (2m, 18 H + 6 H, 3 (CH₂)₄); 2.95-3.35 (m, Me₂N + 3 PhCH₂); 4.30-4.35 (m,

CHOH); 5.20-5.30 (*m*, 2 CHOCO); 7.20-7.40 (*m*, 15 arom. H, NH); 7.77, 8.03 (2*s*, 2 NH). ¹³C-NMR: 23.9, 24.1, 24.1, 24.2, 24.4, 24.5, 35.7, 36.7, 36.8, 37.0, 37.3, 38.0, 38.1, 38.4, 40.2 (15*t*, 3 (CH₂)₄ + 3 PhCH₂); 65.2, 65.9, 66.4 (3*s*, 3 NCCO); 72.3, 74.7, 75.3 (3*d*, 3 CHO); 126.5, 126.8, 126.9, 128.1, 128.2, 128.3, 129.5, 129.7, 129.8 (9*d*, 15 arom. CH); 135.8, 136.6, 137.0 (3*s*, 3 arom. C); 168.5, 170.7, 172.8, 172.8, 173.3, 174.1 (6*s*, 6 C=O). ESI-MS: 845 (100, [M + Na]⁺). Anal. calc. for C₄₇H₅₈N₄O₉ (823.01): C 68.59, H 7.10, N 6.81; found: C 68.51, H 7.19, N 6.59. [α]²⁵_D: -69.3 (c = 1.0, CHCl₃).

2.14. (S)-1-[1-(Dimethylcarbamoyl)cyclopentylcarbamoyl]-2-phenylethyl 1-[(S)-2-{1-[(R)-2-Hydroxy-3-phenylpropanoyl]amino}cyclopentanecarbonyloxy}-3-phenylpropanoyl]amino]cyclopentanecarboxylate (**12b'**): Identical synthesis as described for **12b**, using (R)-**10b** instead of (S)-**10b**. Intermediate compounds have not been characterized. White powder. M.p. 121-123°. IR (KBr): 3398*m*, 3283*s*, 3030*w*, 2957*s*, 2874*w*, 1743*s*, 1649*s*, 1540*s*, 1454*m*, 1264*m*, 1165*s*, 1072*s*, 745*m*, 700*m*. ¹H-NMR: 1.31-1.95, 1.92-2.40 (2*m*, 18 H + 6 H, 3 (CH₂)₄); 2.56-3.23 (*m*, Me₂N + 3 PhCH₂); 4.35-4.40 (*m*, CHOH); 5.28-5.38 (*m*, 2 CHOCO); 7.10-7.35 (*m*, 15 arom. H, NH); 7.70, 8.25 (2*s*, 2 NH). ¹³C-NMR: 23.9, 24.1, 24.40, 24.5, 24.7, 35.8, 37.4, 37.6, 37.7, 38.2, 40.4 (11*t*, 3 (CH₂)₄); 37.0 (*q*, Me₂N); 65.3, 66.1, 66.5 (3*s*, 3 NCCO); 72.5, 74.7 (2*d*, 3 CHO); 126.8, 126.9, 126.9, 128.3, 128.5, 129.1, 129.8 (7*d*, 15 arom. CH); 136.4, 136.5 (2*s*, 3 arom. C); 168.3, 170.65, 172.8, 172.8, 173.4, 174.1 (6*s*, 6 C=O). ESI-MS: 845 (100, [M + Na]⁺). Anal. calc. for C₄₇H₅₈N₄O₉ (823.01): C 68.59, H 7.10, N 6.81; found: C 68.13 H 7.11 N 6.69. [α]²⁵_D: -17.8 (c = 1.0, CHCl₃)

2.15. [(1-{[(1-Dimethylcarbamoyl-1-methyl-2-phenylethyl)carbamoyl]methoxycarbonyl}-1-methyl-2-phenylethyl)carbamoyl]methyl 2-

[(2-Hydroxyacetyl)amino]-2-methyl-3-phenylpropanoate (12c): According to GP 3, **8c** (1.18 g, 3.60 mmol), CDI (583 mg, 3.60 mmol), **11c** (1.74 g, 3.60 mmol), THF (40 ml), 16 h, CC (SiO₂, CH₂Cl₂/MeOH 40:1): 1.19 g (47%) of **12c** (mixture of 4 diastereoisomers). White powder. M.p. 112-115°. IR (KBr): 3275_s, 2943_w, 1750_s, 1655_s, 1548_s, 1256_m, 1110_s, 910_m, 733_m, 703_m. ¹H-NMR: 1.20-1.50 (*m*, 2.5 Me); 1.61, 1.62 (2_s, 0.5 Me) 2.80-4.10 (*m*, Me₂N, 3 PhCH₂, HOCH₂, OH); 4.20-4.95 (*m*, 2 CH₂O); 6.95-7.40 (*m*, 15 arom. H); 7.60-8.00 (*m*, 3 NH). ¹³C-NMR: 21.7, 22.0, 22.1, 22.4, 22.6, 22.8 (6_q, 3 Me); 38.0, 38.3 (2_q, Me₂N); 40.6, 40.7, 41.2, 42.2, 42.5, 42.9, 43.1 (7_t, 3 PhCH₂); 58.4, 58.7, 59.1, 59.2, 59.5, 59.7, 59.8, 60.0, 60.1 (9_s, 3 Ph(Me)C); 61.9, 62.0, 62.6, 63.1, 63.2, (5_t, 3 CH₂O); 126.4, 126.7, 127.3, 127.8, 128.0, 128.3, 128.4, 130.0, 130.1, 130.2, 130.3, 130.4, 130.7, 130.8, 130.9, 131.0 (16_d, 15 arom. CH); 134.6, 134.8, 135.0, 135.1, 135.2, 136.5, 136.6, 136.7, 136.9 (9_s, 3 arom. C); 165.9, 166.1, 166.7, 166.8, 167.9, 168.1, 158.3, 168.4, 168.5, 171.9, 172.0, 172.1, 172.3, 172.4, 172.6, 172.7, 172.8, 172.9 (18_s, 6 C=O). ESI-MS: 725 (85, [M + Na]⁺), 506 (100). Anal. calc. for C₃₈H₄₆N₄O₉ (702.81): C 64.94, H 6.60, N 7.97; found: C 65.32, H 6.22, N 7.85.

2.16. (S)-1-[(1-[(S)-1-[(1-Dimethylcarbamoyl-1-methylethyl)carbamoyl]-2-phenylethoxycarbonyl]-1-methylethyl)carbamoyl]-2-phenylethyl 2-[(2-Hydroxyacetyl)amino]-2-methylpropanoate (**12d**): According to GP 3, **8d** (904 mg, 3.60 mmol), CDI (583 mg, 3.61 mmol), **11a** (1.84 g, 3.60 mmol), THF (40 ml), 8 h, CC (SiO₂, CH₂Cl₂/MeOH 50:1): 2.14 g (91%) **12d**. White powder. M.p. 112-114°. IR: 3402_m, 3281_s, 3066_w, 3021_m, 3009_m, 2941_m, 1745_s, 1652_s, 1545_s, 1497_m, 1471_m, 1455_m, 1440_m, 1388_m, 1367_m, 1342_w, 1291_m, 1268_m, 1146_s, 1082_m, 1064_m, 1031_m, 1001_w, 940_w, 888_w, 842_w. ¹H-NMR: 1.15, 1.29, 1.31, 1.52, 1.54, 1.57 (6_s, 6 Me); 2.90-3.15 (*m*, Me₂N + 1 H of

PhCH₂); 3.20-3.39 (*m*, 1 H of PhCH₂); 3.96, 4.14 (2*d*, *J* = 16.3, CH₂O); 5.20-5.30 (*m*, 2 CHO); 7.10-7.40 (*m*, 10 arom. H); 7.51, 7.79, 8.03 (3*s*, 3 NH). ¹³C-NMR: 24.1, 24.4, 24.9, 25.2, 25.9, 26.2 (6*q*, 6 Me); 37.6, 37.9 (2*t*, 2 PhCH₂); 37.4 (*q*, MeN); 55.6, 56.1, 56.6 (3*s*, 3 Me₂C); 62.1 (*t*, CH₂O); 74.6, 74.9 (2*d*, 2 CHO); 126.8, 127.1, 128.3, 128.4, 129.5, 129.7 (6*d*, 10 arom. CH); 135.9, 136.7 (2*s*, 2 arom. C); 168.8, 179.1, 173.2, 173.2, 173.3, 173.5 (6*s*, 6 C=O). ESI-MS: 677 (100, [*M* + Na]⁺). Anal. calc. for C₃₄H₄₆N₄O₉ (645.75): C 62.37, H 7.08, N 8.56; found: C 61.58, H 7.08, N 8.34. [α]_D²⁵: -33.2 (*c* = 1.0, CHCl₃).

2.17. (S)-1-[1-(Dimethylcarbamoyl)cyclopentylcarbamoyl]-2-phenylethyl 1-[(S)-2-{1-[(S)-2-Hydroxypropanoyl]amino}cyclopentanecarbonyloxy}-3-phenylpropanoyl]amino]cyclopentanecarboxylate (**12e**): According to GP 3, **8e** (1.05 g, 3.60 mmol), CDI (583 mg, 3.61 mmol), **11b** (2.03 g, 3.60 mmol), THF (40 ml), 16 h, CC (SiO₂, CH₂Cl₂/MeOH 45:1): 2.36 g (88%) of **12e**. White powder. M.p. 137-138°. IR (KBr): 3464*m*, 3304*s*, 3062*w*, 3033*w*, 2958*s*, 2874*w*, 1740*s*, 1645*s*, 1547*s*, 1454*m*, 1265*m*, 1164*m*, 1127*w*, 1072*s*, 741*m*, 699*m*. ¹H-NMR: 1.46 (*d*, *J* = 6.8, Me); 1.51-2.42 (*m*, 3 (CH₂)₄); 2.55-2.78, 3.02-3.21 (2*m*, 2 PhCH₂); 2.92 (*s*, Me₂N); 4.26 (*q*, *J* = 6.8, MeCH); 5.30 (*m*, 2 CHO); 7.11-7.32 (*m*, 10 arom. H); 7.49, 7.72, 8.18 (3*s*, 3 NH). ¹³C-NMR: 20.84 (*q*, Me); 24.10, 24.16, 24.28, 24.41, 24.57, 35.68, 36.95, 37.16, 37.25, 37.46, 37.84, 37.98 (12*t*, 3 (CH₂)₄ + 2 PhCH₂); 37.62 (*q*, Me₂N); 65.25, 66.01, 66.44 (3*s*, 3 NCCO); 68.30, 74.50, 74.59 (3*d*, 3 CHO); 126.85, 126.97, 128.36, 128.50, 129.12, 129.77 (6*d*, 10 arom. CH); 136.45, 136.48 (2*s*, 2 arom. C); 168.44, 170.69, 172.84, 173.00, 173.44, 176.12 (6*s*, 6 C=O). ESI-MS: 769 (100, [*M* + Na]⁺). [α]_D²⁵: -36.3 (*c* = 1.2, CHCl₃).

3. *Cyclization Reactions.* – 3.1. (6R,12S,18S)-6,12,18-Tribenzyl-3,3,9,9,15,15-hexamethyl-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone (**14a**): According to GP 4, **12a** (280 mg, 0.4 mmol), toluene (30 ml), CC (SiO₂, CH₂Cl₂/MeOH 60:1): 70 mg (27%) of **14a**. White powder. M.p. 112-113°. IR: 3414_w, 3276_s, 3031_w, 3011_w, 2928_m, 2856_w, 1746_s, 1648_s, 1552_s, 1455_m, 1388_m, 1269_m, 1144_s, 1064_m. ¹H-NMR: 1.19, 1.37, 1.44, 1.44, 1.46, 1.56 (6s, 6 Me); 2.82 (*dd*, *J* = 4.2, 6.9, 1 H of PhCH₂); 3.16 (*dd*, *J* = 2.7, 7.2, 1 H of PhCH₂); 3.33 (*dd*, *J* = 2.4, 6.9, 1 H of PhCH₂); 3.41 (*dd*, *J* = 2.7, 7.2, 1 H of PhCH₂); 3.02-3.05 (*m*, 2 H of PhCH₂); 5.17 (*t*, *J* = 3.3, 1 CHO); 5.22 (*t*, *J* = 3.0, 1 CHO); 5.37 (*dd*, *J* = 2.1, 4.2, 1 CHO); 6.71, 6.96, 6.98 (3s, 3 NH); 7.15-7.30 (*m*, 15 arom. H). ¹³C-NMR: 23.0, 23.6, 24.2, 24.9, 24.9 25.3 (6_q, 6 Me); 36.8, 37.0, 37.5 (3_t, 3 PhCH₂); 56.7, 56.8, 57.6 (3_s, 3 Me₂C); 74.8, 74.9, 75.2, (3_d, 3 CHO); 126.9, 127.0, 127.1, 128.3, 128.4, 128.5, 129.4, 129.7, 129.8 (9_d, 15 arom. CH); 135.1, 135.3, 135.7 (3_s, 3 arom. C); 167.9, 168.1, 168.3, 172.0, 172.5, 173.0 (6_s, 6 C=O). ESI-MS: 722 (100, [*M* + Na]⁺). Anal. calc. for C₃₉H₄₅N₃O₉ (702.81): C 66.94, H 6.48, N 6.00; found: C 66.23, H 6.54, N 5.82. [α]_D²⁵: -25.8 (c 1.8, CHCl₃).

3.2. (6R,12S,18S)-6,12,18-Tribenzyl-3,3,9,9,15,15-tris(tetramethylen)-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone (**14b**): According to GP 4, **12b** (330 mg, 0.4 mmol), toluene (30 ml), CC (SiO₂, CH₂Cl₂/Et₂O 10:1): 78 mg (25%) of **14b**. White powder. M.p. 114-115°. IR: 3427_w, 3318_m, 3021_m, 2964_m, 2878_w, 1744_s, 1680_s, 1529_s, 1497_w, 1454_w, 1236_m, 1165_s, 1071_m. ¹H-NMR: 1.52-2.12, 2.18-2.26, 2.43-2.49 (3_m, 20 H + 3 H + 1 H, 3(CH₂)₄); 2.73 (*dd*, *J* = 4.8, 7.2, 1 H of PhCH₂); 3.00 (*dd*, *J* = 3.3, 6.9, 1 H of PhCH₂); 3.06 (*dd*, *J* = 2.7, 7.2, 1 H of PhCH₂); 3.15 (*dd*, *J* = 3.0,

7.2, 1 H of PhCH₂); 3.33 (*dd*, *J* = 2.4, 7.2, 1 PhCH₂); 3.39 (*dd*, *J* = 2.7, 6.9, 1 H of PhCH₂); 5.20-5.25 (*m*, 2 CHO); 5.30 (*dd*, *J* = 2.4, 4.8, 1 CHO); 6.72 (*s*, 1 NH); 7.10-7.30 (*m*, 15 arom. H, 2 NH). ¹³C-NMR: 23.9, 24.0, 24.6, 24.7, 25.1, 25.2, 31.6, 34.9, 36.1, 36.5, 37.0, 37.0, 37.1, 37.4, 37.9 (15*t*, 3 (CH₂)₄ + 3 PhCH₂); 66.3, 66.9 (2*s*, 3 NCCO); 74.9, 75.0, 75.1 (3*d*, 3 CHO); 126.9, 127.0, 127.1, 128.3, 128.5, 128.5, 129.4, 129.7, 129.8 (9*d*, 15 arom. CH); 135.1, 135.5, 136.1 (3*s*, 3 arom. C); 168.2, 168.3, 168.5, 171.7, 172.7, 173.30 (6*s*, 6 C=O). ESI-MS: 800 (100, [*M* + Na]⁺). Anal. calc. for C₄₅H₅₁N₃O₉ (777.92): C 69.47, H 6.61, N 5.40; found: C 69.12, H 6.70, N 5.27. [α]_D²⁵: -17.2 (*c* = 1.4, CHCl₃).

3.3. *3,9,15-Tribenzyl-3,9,15-trimethyl-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone (14c)*: According to GP 4, **12c** (280 mg, 0.4 mmol), toluene (30 ml), CC (SiO₂, CH₂Cl₂/MeOH 60:1): 121 mg (46%) of **14c** as a mixture of 2 diastereoisomers. White powder. M.p. 88-89°. IR: 3279*s*, 3030*m*, 2977*m*, 1751*s*, 1654*s*, 1523*s*, 1422*s*, 1333*m*, 1112*m*, 1046*m*, 849*w*. ¹H-NMR⁵): 1.24-1.50 (*br. m*, 3 Me); 3.00-3.50 (*br. m*, 3 PhCH₂); 4.10-4.75 (*br. m*, 3 CH₂O); 7.00-7.35 (*m*, 15 arom. H); 7.60-8.00 (*br. m*, 3 NH). ¹³C-NMR (broad signals): 22.4 (*q*, Me); 41.5 (*t*, PhCH₂); 59.4 (*s*, Ph(Me)C); 62.7 (*t*, CH₂O); 126.9, 128.1, 130.5 (3*d*, 15 arom. CH); 135.1 (*s*, 3 arom. C); 168.3, 172.3 (2*s*, 6 C=O). ESI-MS: 680 (100, [*M* + Na]⁺). Anal. calc. for

⁵) ¹H- and ¹³C-NMR-spectra of **14c** and **14d** show broad signals, probably due to the coexistence of different conformers that convert into one another. The same phenomenon has been observed with similar depsipeptides of 18-membered [28] and 24-membered [45][46] ring sizes.

$C_{36}H_{39}N_3O_9 \cdot 0.5 H_2O$ (657.27 \cdot 0.5 H_2O): C 64.85, H 6.05, N 6.30; found: C 64.77, H 6.12, N 6.22.

3.4. *6,12-Dibenzyl-3,3,9,9,15,15-hexamethyl-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone (14d)*: According to GP 4, **12d** (260 mg, 0.4 mmol), toluene (30 ml), CC (SiO_2 , $CH_2Cl_2/MeOH$ 55:1): 105 mg (43%) of **14d** as a mixture of 2 diastereoisomers. White powder. M.p. 159-162°. IR: 3279_s, 3067_w, 3033_w, 2993_m, 2946_m, 2857_w, 1748_s, 1650_s, 1554_s, 1471_m, 1455_m, 1388_m, 1368_w, 1308_m, 1266_m, 1140_s, 1065_m, 909_m. 1H -NMR⁴): 1.08-1.70 (br. *m*, 6 Me); 2.80-3.45 (br. *m*, 2 $PhCH_2$); 4.00-4.80 (br. *m*, CH_2O); 5.10-5.50 (br. *m*, 2 CHO); 7.00-7.35 (*m*, 10 arom. H); 7.50-8.30 (br. *m*, 3 NH). ^{13}C -NMR (br. signals): 23.7 (*q*, 6 Me); 37.5 (*t*, 2 $PhCH_2$); 56.1 (*s*, NCCO); 63.3 (*t*, CH_2O); 74.9 (*d*, 2 CHO); 126.9, 128.3, 129.4 (3*d*, 10 arom. CH); 136.2 (*s*, 2 arom. C); 170.5, 173.4 (2*s*, 6 C=O). ESI-MS: 632 (100, $[M + Na]^+$). Anal. calc. for $C_{32}H_{39}N_3O_9$ (609.67): C 63.04, H 6.45, N 6.89; found: C 62.88, H 6.77, N 6.93. $[\alpha]_D^{25}$: -31.9 (*c* = 1.2, $CHCl_3$).

3.5. *6,12-Dibenzyl-18-methyl-3,3,9,9,15,15-tris(tetramethylen)-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone (14e)*: According to GP 4, **12e** (250 mg, 0.34 mmol), toluene (30 ml), CC (SiO_2 , $CH_2Cl_2/MeOH$ 45:1): 79 mg (33%) of **14e**. White powder. M.p. 134-135°. IR (KBr): 3426_w, 3298_m, 2959_m, 2875_w, 1745_s, 1659_s, 1545_s, 1453_m, 1301_m, 1239_s, 1166_s, 1073_m, 746_m, 700_m. 1H -NMR: 1.48 (*d*, *J* = 6.7, Me); 1.49-2.57 (*m*, 3 $(CH_2)_4$); 2.74 (*dd*, *J* = 9.7, 14.1, 1 H of $PhCH_2$); 3.13-3.39 (*m*, 3 H of $PhCH_2$); 6.54 (br. *s*, NH); 7.11-7.38 (*m*, 10 arom. H + 2 NH). ^{13}C -NMR: 17.6 (*q*, Me); 23.9, 24.0, 24.4, 24.5, 25.3, 25.5, 34.8, 36.3, 36.4, 36.5, 36.9, 37.3, 37.5, 37.9 (14*t*, 3 $(CH_2)_4$ + 2 $PhCH_2$); 66.2, 66.3, 66.8 (3*s*, 3 NCCO); 71.4, 74.9, 75.0 (3*d*, 3 CHO);

126.8, 127.1, 128.4, 128.5, 129.2, 129.6 (6d, 10 arom. CH); 134.9, 136.1 (2s, 2 arom. C); 168.2, 168.5, 169.6, 171.5, 172.4, 173.5 (6s, 6 C=O). ESI-MS: 724 (100, $[M + Na]^+$). $[\alpha]_D^{25}$: -16.8 (c = 1.0, CHCl₃).

4. *Control Experiments.* – 4.1. *8-Benzyl-9-oxa-6-azaspiro[4.5]decane-7,10-dione* (**16**): According to GP 4, **10b** (152 mg, 0.5 mmol), toluene (30 ml), CC (SiO₂, CH₂Cl₂/Et₂O 10:1): 66 mg (51%) of racemic **16**. White powder. M.p. 106-107°. IR (KBr): 3189m, 3086m, 2964m, 2926m, 2880w, 1741s, 1679s, 1454m, 1436m, 1346m, 1261m, 1185m, 1093m, 1021w, 828m, 740w, 694m. ¹H-NMR ((D)₆-DMSO): 1.44-2.15 (m, (CH₂)₄); 3.07 (dd, *J* = 7.5, 14.7, 1 H of PhCH₂); 3.31 (dd, *J* = 4.0, 14.7, 1 H of PhCH₂); 5.31 (dd, *J* = 4.0, 7.5, CHO); 7.25-7.41 (m, 5 arom. H); 8.76 (br. s, NH). ¹³C-NMR: 23.9, 24.3, 36.4, 38.0, 39.8 (5t, (CH₂)₄ + PhCH₂); 63.6 (s, NCCO); 77.8 (d, CHO); 126.5, 128.1, 129.6 (3d, 5 arom. CH); 136.1 (s, arom. C); 166.2, 171.0 (2s, 2 CO). ESI-MS: 282 (100, $[M + Na]^+$). Anal. calc. for C₁₅H₁₇NO₃ (259.31): C 69.47, H 6.61, N 5.40; found: C 69.50, H 6.78, N 5.38.

4.2. *(S)-N-Butyl-2-hydroxy-3-phenylpropanamide* (**15**): To a soln. of *(S)*-phenyllactic acid (300 mg, 1.81 mmol) and 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 2 mmol, 760 mg) in CH₂Cl₂ (10 ml) was added butylamine (396 mg, 0.54 ml, 5.5 mmol). After 4 h stirring at r.t., H₂O (10 ml) was added. The org. layer was washed with 0.5M HCl (3 x 5 ml) and sat. aq. NaHCO₃-soln. (3 x 5 ml), and dried (MgSO₄). Evaporation of the solvent and CC yielded **15** (288 mg, 72%). White powder. M p. 83-84°. IR (KBr): 3335s, 2962m, 2934m, 2875w, 1627s, 1556s, 1411m, 1292m, 1084s, 729m, 699m. ¹H-NMR: 0.89 (t, *J* = 7.2, Me); 1.21-1.47 (m,

MeCH₂CH₂); 2.81-2.94 (*m*, 1 H of PhCH₂); 3.14-3.30 (*m*, CH₂N + 1 H of PhCH₂ + OH); 4.26 (*m*, CHO); 6.46 (br. *s*, NH); 7.20-7.33 (*m*, 5 arom. H). ¹³C-NMR: 13.6 (*q*, Me); 19.9, 31.4, 38.7, 40.8 (4*t*, 4 CH₂); 72.7 (*d*, CHO); 126.9, 128.6, 129.6 (3*d*, 3 arom. CH); 137.1 (*s*, arom. C); 172.8 (*s*, C=O). ESI-MS: 244 (100, [M + Na]⁺). [α]_D²⁵: -43.3 (*c* = 1.1, CHCl₃).

5. *X-Ray Crystal-Structure Determination of 14a* (Table and Figure)⁶. All measurements were performed on a *Nonius KappaCCD* area-detector diffractometer [52] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream* 700 cooler. The data collection and refinement parameters are given in the Table, and a view of the molecule is shown in the Figure. Data reduction was performed with *HKL Denzo* and *Scalepack* [53]. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Equivalent reflections were merged. The structure was solved by direct methods using *SIR92* [54], which revealed the positions of all non-H-atoms. There are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program *PLATON* [55], but none could be found. The non-H-atoms were refined anisotropically. The amide H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and

⁶) CCDC-..... contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre*, via www.ccdc.cam.ac.uk/data_request/cif.

refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{\text{eq}}$ of its parent C-atom ($1.5U_{\text{eq}}$ for the Me groups). The refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\sum w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Nine reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from [56a], and the scattering factors for H-atoms were taken from [57]. Anomalous dispersion effects were included in F_c [58]; the values for f' and f'' were those of [56b]. The values of the mass attenuation coefficients are those of [56c]. All calculations were performed using the *SHELXL97* [59] program.

Table. *Crystallographic Data for Compound 14a*

References

- [1] K. W. Li, J. Wu, W. Xing, J. A. Simpson, *J. Am. Chem. Soc.* **1996**, *118*, 7237.
- [2] Y. Hirai, K. Yokota, T. Momose, *Heterocycles* **1994**, *39*, 603.
- [3] S. Cerrini, E. Gavuzzo, G. Luisi, F. Pinnen, *Int. J. Pept. Protein Res.* **1993**, *41*, 282.
- [4] A. M. Sefler, M. C. Kozlowski, T. Guo, P. A. Bartlett, *J. Org. Chem.* **1977**, *62*, 93.
- [5] Y. L. Dory, J. M. Mellor, J. F. McAleer, *Tetrahedron Lett.* **1996**, *52*, 1343.
- [6] T. Imaeda, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1994**, *35*, 591.

- [7] J. S. Davies, *J. Peptide Sci.* **2003**, 9, 471.
- [8] G. E. Schulz, R. H. Schirmer, *Principles of Protein Structure*, Springer, New York 1979.
- [9] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1984**, 67, 526.
- [10] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1987**, 70, 329.
- [11] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1990**, 73, 221.
- [12] J. M. Villagordo, H. Heimgartner, *Helv. Chim. Acta* **1997**, 80, 748.
- [13] K. N. Koch, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2000**, 83, 233.
- [14] K. N. Koch, A. Linden, H. Heimgartner, *Tetrahedron* **2001**, 57, 2311.
- [15] K. N. Koch, H. Heimgartner, *Helv. Chim. Acta* **2000**, 83, 1881.
- [16] K. N. Koch, G. Hopp, A. Linden, K. Moehle, H. Heimgartner, *Helv. Chim. Acta* **2001**, 84, 502.
- [17] H. Heimgartner, F. S. Arnhold, S. P. Fritschi, K. N. Koch, J. E. F. Magirius, A. Linden, *J. Heterocycl. Chem.* **1999**, 36, 1539.
- [18] B. Iliev, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003**, 86, 3215.
- [19] B. Iliev, A. Linden, R. W. Kunz, H. Heimgartner, *Tetrahedron* **2006**, 62, 1079.
- [20] B. Iliev, Ph.D. thesis, Universität Zürich, 2005.
- [21] N. S. Wulfson, V. A. Puchkov, V. N. Bochkarev, B. V. Rozinov, A. M. Zayakoon, M. M. Shemyakin, Y. A. Ovchinnikov, V. T. Ivanov, A. A. Kiryushkin, E. I. Vinogradova, M. Y. Feigina, N. A. Aldanova, *Tetrahedron Lett.* **1964**, 5, 951.

- [22] N. S. Wulfson, V. A. Puchkov, B. V. Rozinov, A. M. Zayakoon, M. M. Shemyakin, Y. A. Ovchinnikov, A. A. Kiryushkin, V. T. Ivanov, *Tetrahedron Lett.* **1965**, 6, 2793.
- [23] K. Brockmann, G. Schmidt-Kastner, *Chem. Ber.* **1955**, 88, 57.
- [24] M. M. Shemyakin, N. A. Aldanova, R. I. Vinogradova, V. Y. Feigina, *Tetrahedron Lett.* **1963**, 28, 1921.
- [25] B. C. Pressman, E. J. Harris, W. S. Jagger, J. N. Johnson, *Procl. Nat. Acad. Sci. U.S.A.* **1967**, 58, 1949.
- [26] Y. A. Ovchinnikov, V. T. Ivanov, A. V. Evstratov, I. I. Mikhaleva, V. F. Bystrov, S. L. Portnova, T. A. Balashova, E. N. Meshcheryakova, V. M. Tul'chinskii, *Int. J. Pept. Protein Res.* **1974**, 6, 465.
- [27] B. C. Pressman, *Ann. Rev. Biochem.* **1976**, 45, 501.
- [28] J. E. F. Magirius, Ph.D. thesis, Universität Zürich, 1995.
- [29] H. Heimgartner, *Angew. Chem., Int. Ed.* **1991**, 30, 238.
- [30] P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1990**, 73, 13.
- [31] W. Altherr, Ph.D. thesis, Universität Zürich, 1994.
- [32] R. Luykx, C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1996**, 79, 527.
- [33] R. T. N. Luykx, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003**, 86, 4093.
- [34] N. Pradeille, H. Heimgartner, *J. Peptide Sci.* **2003**, 9, 827.
- [35] N. Pradeille, O. Zerbe, K. Möhle, A. Linden, H. Heimgartner, *Chem. Biodiv.* **2005**, 2, 1127.
- [36] J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1998**, 54, 8721.

- [37] J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1999**, *55*, 5359.
- [38] J. Lehmann, A. Linden, H. Heimgartner, *Helv. Chim. Acta.* **1999**, *82*, 888.
- [39] J. Lehmann, A. Linden, H. Heimgartner, *Helv. Chim. Acta.* **1999**, *82*, 1899.
- [40] F. S. Arnhold, Ph.D. thesis, Universität Zürich, 1997.
- [41] T. Jeremic, A. Linden, K. Moehle, H. Heimgartner, *Tetrahedron* **2005**, *61*, 1871.
- [42] T. Jeremic, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2004**, *87*, 3056.
- [43] T. Jeremic, A. Linden, H. Heimgartner, *Chem. Biodiv.* **2004**, *1*, 1730.
- [44] I. Philipova, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2005**, *88*, 1711.
- [45] P. Köttgen, A. Linden, H. Heimgartner, in preparation.
- [46] P. Köttgen, Ph.D. thesis, universität Zürich, 2006.
- [47] C. K. Johnson, ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
- [48] J. Bernstein, R. E. Davis, L. Shimoni, N.-L. Chang, *Angew. Chem., Int. Ed.* **1995**, *34*, 1555.
- [49] K. C. Nicolaou, *Tetrahedron* **1977**, *33*, 683.
- [50] Y. Yamashita, S. Saito, H. Ishitani, S. Kobayashi *J. Am. Chem. Soc.* **2003**, *125*, 3793.
- [51] J. J. Wen, C. M. Crews, *Tetrahedron Lett.* **1998**, *39*, 77.
- [52] R. Hooft, *KappaCCD Collect Software*, Nonius BV, Delft, The Netherlands, 1999.
- [53] Z. Otwinowski, W. Minor, in 'Methods in Enzymology', Vol. 276, 'Macromolecular Crystallography', Part A, Eds. C. W. Carter Jr., R. M. Sweet, Academic Press, New York, 1997, p. 307.

- [54] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *SIR92, J. Appl. Crystallogr.* **1994**, 27, 435.
- [55] A. L. Spek, PLATON, Program for the Analysis of Molecular Geometry, University of Utrecht, the Netherlands, 2003.
- [56] a) E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 6.1.1.1, p. 477; b) D. C. Creagh, W. J. McAuley, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 4.2.6.8, p. 219; c) D. C. Creagh, J. H. Hubbell, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 4.2.4.3, p. 200.
- [57] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, 42, 3175.
- [58] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, 17, 781.
- [59] G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

Table. *Crystallographic Data for Compound 14a*

Crystallized from	hexane/CH ₂ Cl ₂
Empirical formula	C ₃₉ H ₄₅ N ₃ O ₉
Formula weight [g mol ⁻¹]	699.80
Crystal color, habit	colorless, needle
Crystal dimensions [mm]	0.07 × 0.10 × 0.30
Temperature [K]	160(1)
Crystal system	monoclinic
Space group	<i>P</i> 2 ₁
<i>Z</i>	4
Reflections for cell determination	6575
2 θ range for cell determination [°]	4–50
Unit cell parameters <i>a</i> [Å]	11.3280(1)
<i>b</i> [Å]	24.3225(3)
<i>c</i> [Å]	13.7975(2)
β [°]	90.0072(6)
<i>V</i> [Å ³]	3801.56(8)
<i>F</i> (000)	1488
<i>D_x</i> [g cm ⁻³]	1.223
μ (MoK α) [mm ⁻¹]	0.0870
Scan type	ω
2 $\theta_{\text{(max)}}$ [°]	50
Total reflections measured	34567
Symmetry independent reflections	6886
Reflections with <i>I</i> > 2 σ (<i>I</i>)	4833
Reflections used in refinement	6877
Parameters refined; restraints	956; 1
Final <i>R</i> (<i>F</i>) [<i>I</i> > 2 σ (<i>I</i>) reflections]	0.0416
<i>wR</i> (<i>F</i> ²) (all data)	0.1007
Weights:	$w = [\sigma^2(F_o^2) + (0.0514P)^2]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.000
Secondary extinction coefficient	0.0079(7)
Final $\Delta_{\text{max}}/\sigma$	0.001
$\Delta\rho$ (max; min) [e Å ⁻³]	0.32; -0.19

Legend

Figure. *ORTEP Plot* [47] of the molecular structure of one of the symmetry-independent molecules of **14a** (30% probability ellipsoids; arbitrary numbering of atoms, most H-atoms omitted for clarity).